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National Cancer Institute

Bone Marrow Transplantation

Research Report

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Introduction

Recent advances in scientific knowledge and technology have made bone marrow transplantation a viable treatment for some patients with leukemia, lymphoma, aplastic anemia, severe combined immunodeficiency syndrome, and certain inherited blood disorders such as thalassemia. A bone marrow transplant replaces a patient's abnormal or diseased marrow with healthy marrow from a donor.

This *Research Report* discusses the bone marrow transplantation procedure and possible complications, current research in the field, and diseases that can be treated with bone marrow transplants. The information was obtained from recent articles in the scientific literature.

Description and Function of the Bone Marrow

The large human bones are made up of hard, dense, bony tissue around a core of spongy tissue. Spongy bone contains many large spaces filled with marrow. This bone marrow produces three types of bloods cells: leukocytes (white blood cells); erythrocytes (red blood cells); and platelets (clotting cells).

Leukocytes help defend the body against infection. Leukocytes are made up of three lines of white blood cells: granulocytes, lymphocytes, and a cell line that includes monocytes and macrophages. Neutrophils are the most common type of granulocyte and play a major role in fighting infections by engulfing and digesting bacteria. Lymphocytes are further divided into B cells, which produce antibodies, and T cells, which attack virus-infected cells, foreign tissue, and cancer cells.

Erythrocytes carry oxygen from the lungs to all tissues of the body, and then pick up carbon dioxide as a waste product to be carried back to the lungs and breathed out. This function is made possible by iron-rich hemoglobin in the red blood cells.

Platelets (also called thrombocytes) prevent bleeding by initiating a chain of reactions that form blood clots. Platelets are small cell fragments derived from a larger cell called a megakaryocyte.

Diseases Treated with Bone Marrow Transplants

Bone marrow transplantation may be part of the treatment for several kinds of leukemia and lymphoma, which are types

of cancer. Marrow transplants also can help patients with several noncancerous disorders: aplastic anemia, severe combined immunodeficiency disease, and thalassemia.

Leukemia

Leukemia is a cancer that arises in the blood-forming cells. Immature, abnormal white blood cells, unable to perform their infection-fighting roles, begin filling the bone marrow and spilling into the bloodstream. Leukemia cells cannot do the work of normal cells. These abnormal cells also reduce the production of normal red blood cells and platelets. As a result, patients with leukemia are often anemic and prone to bleeding. Other symptoms may include easy bruising, fever, weakness, chronic fatigue, recurrent infections, and pain in joints and bones.

A diagnosis of leukemia is made by blood tests and a bone marrow biopsy. Treatment usually starts immediately, and usually involves chemotherapy designed to destroy leukemia cells directly or to block their ability to reproduce. Supportive therapy may include antibiotics, radiation therapy, and transfusions of granulocytes and platelets.

Additional information on leukemia is available in publications listed in "Suggestions for Additional Reading" at the end of this *Report*.

Bone marrow transplants can be part of the treatment for several types of leukemia: acute lymphocytic leukemia (ALL), acute nonlymphocytic leukemia (ANLL), and chronic myelocytic leukemia (CML). Lymphocytic leukemia affects the lymphocytes, and nonlymphocytic leukemia affects other cell lines, like the neutrophils or monocytes. Chronic myelocytic leukemia affects the granulocytes. Many successful transplants have been performed on patients with each of these types of leukemia. Generally, transplants performed in the earlier phases of leukemia have a higher success rate than those performed in patients with advanced disease that has become resistant to anticancer drugs.

Lymphoma

Lymphoma is a term used for any cancer that develops in the lymphoid tissue, which includes lymph nodes, lymph vessels, the spleen and the thymus. There are several types of lymphomas, including Hodgkin's disease and a number of non-Hodgkin's lymphomas. A diagnosis of lymphoma is usually established by the surgical removal and microscopic examination of lymphoid tissue. Hodgkin's disease and several other types of lymphoma can be treated successfully with radiation or combinations of anticancer drugs. In certain cases where large doses of radiation offer increased chances for effective therapy, bone marrow transplants make the high-dose treatment possible by replacing marrow destroyed by the radiation.

Additional information on lymphoma is available in publications listed in the "Suggestions for Additional Reading" at the end of this *Report*.

Aplastic Anemia

In aplastic anemia, the bone marrow is unable to produce all the necessary blood cells. The disease is often fatal despite conventional treatments. Bone marrow transplantation thus offers a way to treat this otherwise incurable condition.

Immunological Diseases

Severe combined immunodeficiency disease (SCID) is the deadliest of the immunodeficiency diseases. SCID patients lack all of the body's natural immune defenses and are thus unable to ward off diseases. These patients are often placed in a germ-free protective environment. Bone marrow transplantation has cured SCID in some patients, and is the only known cure for SCID at present. The procedure is not possible with all patients, however, and is not always successful.

Thalassemia

Thalassemia is an inherited blood disorder characterized by abnormal hemoglobin in the red blood cells. As a result, the red blood cells are stunted and do not carry oxygen efficiently. Symptoms include shortness of breath, severe pallor, and chronic fatigue. The disease is fatal in 2 to 3 years if untreated. Although other treatments can extend a patient's life by many years, bone marrow transplantation has cured the disorder in some of the patients where the technique has been possible.

Bone Marrow Transplantation Procedure

The steps involved in a bone marrow transplant may vary from one medical center to another. Various details also may change as research continues. A transplant will generally include the following steps:

Patient Selection and Consent

When patients and physicians consider bone marrow transplantation as a treatment option, they must evaluate factors such as the patient's specific illness, age, and medical history; other treatments that might have been tried earlier; and the possible risks and benefits of a transplant in the patient's particular case. Some types of leukemia and lymphoma, for example, are curable in many cases with anticancer drugs (chemotherapy) and/or radiation therapy. These treatments would be tried before bone marrow transplantation is considered.

The complications and risks of marrow transplantation are discussed later in this *Report,* and should be given serious consideration. Some complications, particularly infections and graft-versus-host disease, can be life-threatening. Physicians discuss these matters with patients and marrow donors before consent is given to go ahead with the procedure.

Selection of the Donor

Ideal donors are identical twins, because the identity includes the immune system's signals for recognizing a graft as being "self" or "foreign." When an identical twin is the donor, there is no risk that the patient will reject the graft or that the leukocytes of the donated marrow will react against the patient. Because most patients do not have identical twins, however, transplants usually have been performed with other family members. Studies with animals have shown that a graft is more likely to "take" if certain proteins on the surface of white blood cells are the same with both the donor and the recipient. In humans, these proteins are called HLA antigens. HLA antigens are inherited from the parents, one set from the mother and one from the father. There is thus a 25 percent chance that any one brother or sister will be HLA-identical to the patient.

There are three different kinds of grafts, depending on the source of the marrow. An *autologous* graft is the patient's own marrow, removed before the patient is given treatment with chemotherapy and/or radiation that may destroy the remaining marrow. The removed marrow also may be treated before being retransplanted in the patient. A *syngeneic* graft comes from an identical twin and is genetically identical to the patient. To date, syngeneic grafts have been the most successful. An *allogeneic* graft comes from a sibling or parent. These grafts, which are the most common type, have the greatest chance of success when the donor and recipient are HLA-identical.

Preparation of the Patient

Unless the patient totally lacks a functioning immune system, the patient must be given some type of immunosuppressive treatment before the donor marrow can be infused. The treatment is intended to keep the patient's immune system from rejecting the "foreign" marrow. Radiation and a high dose of cyclophosphamide (Cytoxan) are commonly used. If the patient has leukemia or other types of cancer, high-dose chemotherapy will be given to destroy cancer cells in the marrow and elsewhere. This is usually followed by a total of 1,000 to 1,500 rad of radiation over the entire body, to penetrate the bones and kill leukemia cells in the marrow. The radiation treatment is often given in smaller doses over the course of several days to minimize the risk of side effects.

For patients with aplastic anemia, large doses of cyclophosphamide commonly are given before the transplant to suppress the immune response. If the aplastic anemia patient has had many blood transfusions, other procedures may be added.

Infusion of the Marrow

The bone marrow transplant procedure begins with aspiration of the marrow from the donor. In an operating room with the donor under general or spinal anesthesia, marrow is taken from the pelvic bone with a needle and syringe. A number of aspirations are taken to avoid dilution of the marrow with blood. From 500 to 800 milliliters of marrow and blood cells are usually obtained. After the aspirations, a unit of blood, which had been taken from the donor a week before, is returned to the donor to prevent anemia. The donor may feel some pain

and stiffness at the aspiration site for a few days.

The marrow is passed through stainless steel screens to break up particles. It is then injected into the patient intravenously. The marrow cells enter the general circulation and migrate through the blood to marrow cavities in the patient's bones. The cells begin to grow in the marrow and produce new white blood cells, red blood cells, and platelets.

Supportive Care

Because 2 to 4 weeks or longer may pass before the marrow begins producing new blood cells, the patient needs intensive supportive care. Infections must be prevented. Patients and visitors use face masks and hand-washing to minimize exposure to bacteria. The patient is given antibiotics and sometimes is placed in the sterile environment of a laminar air-flow room.

Transplant patients may receive granulocyte transfusions to help prevent infection when their granulocyte level falls below 200 cells per cubic millimeter of blood. The granulocyte donor is usually the marrow donor or another closely matched family member. At any sign of infection by viruses, fungi or bacteria, granulocytes may be given until the patient's own marrow can begin to produce enough of these white blood cells.

The patient receives red blood cells to prevent anemia. If the hematocrit (a measure of the concentration of red cells in the blood) falls below a certain level, whole blood transfusions are given.

Transfusions of platelets help keep the platelet level above 20,000 per cubic millimeter and thus prevent uncontrolled internal or external bleeding. Some patients do not respond to platelets donated from random donors. When this occurs, family members donate platelets.

All blood products given to transplant patients are treated with approximately 1,500 rad of radiation. This inactivates lymphocytes from the donor, which could cause an immune reaction against the patient.

Adequate nutrition is another important supportive measure. Preparation for the transplant often causes nausea, vomiting, and irritation of the linings of the mouth and the gastrointestinal tract. The patient thus may have trouble eating for several weeks. As an alternative method of nutritional support, the patient can be given a complete diet in the form of nutrients dissolved in intravenous fluids given through a Hickman catheter that was inserted in a large vein when the patient was admitted for the transplant. This is called "total parenteral nutrition." The catheter also can be used for giving blood products, antibiotics, and other drugs, as well as for withdrawing blood samples. Use of the catheter avoids the multiple needle pricks associated with lengthy treatment. Although some catheters eventually have to be removed due to infection, most can be kept in place for up to 3 months.

A rise in the number of granulocytes and platelets is usually a sign that the graft has "taken." Gene markers in the blood and cytogenetic studies are among tests used to confirm that the donor marrow is growing.

Possible Complications

Infection

Because the patient's white blood cell count is low and defenses against infection are poor during the first 2 to 4 weeks after transplant, he or she is at high risk for viral, fungal, and bacterial infections. Mucositis, herpes simplex, and herpes zoster are common problems. With current antibacterial therapy and granulocyte transfusions, bacterial infections account for fewer than 10 percent of deaths associated with bone marrow transplantation. Despite the use of antifungal drugs like amphotericin, fungal infections have caused a high rate of illness and about 15 percent of deaths.

Interstitial pneumonia is another major cause of illness and death. About half the pneumonias are caused by cytomegalovirus infections, which have been fatal in about 80 percent of the cases. This is the most common cause of death in transplant patients.

Bleeding

When the patient's platelet count is low, nosebleeds and bleeding gums can be frequent. More serious bleeding can also occur. Treatment is with platelet transfusions.

Liver Disease

Liver disease is another problem that may occur in the months following a bone marrow transplant. Possible causes include

toxic effects of drugs and radiation, obstructed veins in the liver, viral hepatitis, fungal and bacterial infections, and graft-versus-host disease. Many of these conditions are reversible and treatable.

Rejection

Although rejection of a marrow graft is relatively rare in leukemia patients, it occasionally occurs in patients with aplastic anemia who have been treated previously with blood transfusions. The transfusions appear to make the patient's immune system unusually reactive against antigens of the donated marrow that are not involved in the matching of HLA antigens. For this reason, marrow transplants should be carried out before blood transfusions have been given.

Relapse

For acute nonlymphocytic leukemia patients who receive transplants while they are in first remission, the rate of leukemia recurrence has been 10 to 15 percent. Patients with all other types of leukemia who have relapsed at least once before the transplant have had a recurrence rate of 50 to 65 percent.

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) is the reaction of the donor marrow against the tissue of the host patient. It occurs because the transplanted white blood cells recognize the host organs as "foreign," even though the white blood cell types are the same. GVHD chiefly affects the skin, liver, and gastrointestinal tract. Symptoms can range from mild to severe, and GVHD can be fatal. The most common symptoms are skin rashes, jaundice, liver disease, and diarrhea.

Chronic GVHD has occurred in about one-fourth of all long-term survivors. It is associated with abnormal pigmentation of the skin, and a hardening and thickening of patches of skin and the layers of tissue under the skin. The mouth and surface of the eye may dry out. Occasionally the esophagus, gut, or liver is affected. Bacterial infections and weight loss are common. Early and prolonged treatment with corticosteroids and other drugs is effective in a majority of patients.

To reduce the chances that GVHD will occur, patients routinely receive a drug called methotrexate after transplant.

Still, about 50 percent of the patients have developed GVHD. About 30 percent get it in a severe form, and it is life-threatening in about 20 percent of these severe cases. Other steps taken to prevent or treat the severe form of GVHD may include high-dose steroids such as prednisone, antithymocyte globulin, and cyclosporine. About one-third of the patients respond, but not always to the same treatment. Of those patients who get acute GVHD, about half will improve after treatment.

Older patients and patients who receive transplants from donors who are not HLA-matched are more likely to develop GVHD.

Current Research and Advances

In recent years significant advances have been made in marrow transplantation, and many transplant teams around the world are investigating new techniques to improve results even more.

Several discoveries may make possible the use of an unrelated donor or a partially HLA-matched donor. The implications of this are immense, because 60 to 70 percent of patients with leukemia or other blood and immune diseases do not have relatives whose tissues are HLA-identical to theirs. One approach uses lectins, substances found in soybeans, which clump together with mature T cells when the two are mixed. T cells are the white blood cells that are mainly responsible for GVHD. Marrow is aspirated from the donor, mixed with lectins, and then placed on top of a thick substance, such as albumin, in a test tube. The aggregates of T cells and lectins sink to the bottom because they are heavier. Although the remaining marrow cells are almost entirely free of T cells, they are purified again by mixing them with red blood cells of sheep, which bind with any remaining T cells. The purified marrow is then given to the patient.

Another technique uses specially prepared antibodies, called monoclonal antibodies, to attack mature T cells and eliminate them from a marrow sample. If T cells remain, investigators may try to destroy them by giving the monoclonal antibodies directly to the patient.

Autologous transplants are another highly experimental procedure. Use of the patient's own marrow carries with it the risk that the marrow may be con-

taminated with cancer cells. Therefore, techniques to "cleanse" the removed marrow of cancer cells are under study. These include the use of:

- monoclonal antibodies prepared against cancer cells, either alone or with added complement, a complex of proteins that are part of the body's normal immune response;
- monoclonal antibodies combined with cell-destroying toxins such as ricin or linked with magnetic particles that permit the removal of cancer cells with a magnet;
- centrifugation to remove cancer cells by spinning at ultra-high speeds;
- anticancer drugs.

After the patient is treated with intensive chemotherapy and radiotherapy in an effort to kill all cancer cells in the patient's body, the purified marrow can be returned to the patient.

Studies are also examining the possibility of establishing a donor bank to collect marrow samples from donors in the general population. Tissue typing would match this donated marrow with unrelated recipients who need marrow transplants.

It may be possible to expand the application of bone marrow transplants to other disorders such as small cell cancer of the lung, testicular cancer, breast and ovarian cancers, and inherited marrow and blood disorders like sickle cell disease.

PDQ

The National Cancer Institute has developed PDQ (Physician Data Query), a computerized database designed to give doctors quick and easy access to:

- The latest treatment information for most types of cancer;
- Descriptions of clinical trials that are open for patient entry; and
- Names of organizations and physicians involved in cancer care.

To get access to PDQ, a doctor may use an office computer with a telephone hookup and a PDQ access code, or the services of a medical library with on-line searching capability. Most Cancer Information Service offices (1-800-4-CANCER) provide a physician with one free PDQ search, and can tell doctors how to get regular access to the database. Patients may ask their doctor to use PDQ or may call 1-800-4-CANCER themselves. Information specialists at this toll-free number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, and treatment.

Conclusion

Although bone marrow transplantation has become the treatment of choice for certain stages of some diseases, it is still a complex procedure and should only be undertaken in medical centers with experienced staff and adequate resources. Research is needed to understand more about the complications of bone marrow transplants, the possibilities for marrow transplants from unrelated donors, and the uses of transplantation in other diseases. Bone marrow transplantation has been shown to improve long-term survival for patients with diseases such as acute leukemia and aplastic anemia. It offers the hope of saving lives of other patients with life-threatening disorders.

Questions To Ask Your Doctor

Answers to the following questions might help patients who are considering having a bone marrow transplant.

Is a bone marrow transplant the best option for treatment of my condition?

What are the chances that the donated marrow will not grow in me?

With my condition, what are my chances of becoming completely cured?

What are the risks and possible side effects of a bone marrow transplant?

What is the cost of a marrow transplant, and how does it compare with the cost of other possible therapy?

How long will I have to stay in the hospital? How long will I be treated as an outpatient?

What are some of the risks and side effects of the radiation and chemotherapy used to prepare me for transplantation?

Will I be able to resume normal activities after transplantation?

If a transplant is done, will I need other treatment?

After the transplant, how often will I need medical checkups?

Because of the risk of infection, will I be able to have friends and family visit me in the hospital?

Glossary of Terms

Allogeneic—Genetically different, as in distinguishing a patient from a relative.

Anemia—A condition in which there is a decreased number of red cells, which results in weakness and fatigue.

Antithymocyte globulin (ATG)—A protein preparation used to treat and prevent graft-versus-host disease.

Aspiration—The removal of the marrow from the marrow cavities by suction.

Autologous—A graft or tissue from the same source; that is, taken from the patient and then returned to the patient.

Chemotherapy—Treatment with anticancer drugs.

Cyclophosphamide—A drug used for immunosuppression and destruction of leukemia cells. A commonly used brand name is Cytoxan.

Cyclosporine—A drug used to treat and prevent graft-versus-host disease.

Cytogenetics—The study of the origin, structure, and function of the chromosomes in the blood cells.

Cytomegalovirus—A viral infection that can cause serious illness in immunosuppressed patients.

Dyspigmentation—Abnormal coloration of the skin.

Engraftment—The successful implantation of donor marrow in the patient's marrow cavities.

Genetic markers—Various characteristics linked with a person's genes, which help to determine if blood cells produced by the marrow are coming from the donor's marrow.

Granulocyte—One of the major groups of white blood cells. They are also called polymorphonuclear cells or myeloid cells. Granulocytes include neutrophils, eosinophils, and basophils.

Herpes simplex—A viral infection that usually produces small, temporary, irritating and sometimes painful fluid-filled blisters on the skin and mucous membranes.

Herpes zoster—A viral infection that produces shingles, painful skin eruptions that follow the underlying route of nerves inflamed by the virus.

Hickman catheter—A catheter designed for long-term use in giving drugs and total parenteral nutrition, and in withdrawing blood samples.

Histocompatibility—The state of similarity between tissues of the donor and the recipient.

Immunosuppression—Reduction of the functions of the immune system to prevent a reaction against donor marrow cells and to prevent graft-versus-host disease.

Interstitial pneumonia—Inflammation of the lung tissue, often caused by a virus.

Laminar air-flow room—A room with one-way air flow from a sterile source, which helps prevent the spread of airborne bacteria and viruses.

Leukocyte—The term for all the types of white blood cells.

Lymphocyte—One of the major groups of white blood cells. B lymphocytes make antibodies against bacteria and other foreign substances in the body; T lymphocytes attack virus-infected cells and other foreign cells directly.

Methotrexate—A drug used to treat and prevent graft-versus-host disease.

Mucositis—Inflammation of the mucous membranes.

Neutrophil—The most common type of white blood cell in the bloodstream.

Prednisone—A hormone-like drug used to treat and prevent graft-versus-host disease.

Steroids—Drugs used to treat and prevent graft-versus-host disease.

Subcutaneous tissue—Tissue beneath the skin.

Syngeneic—Genetically identical, as from an identical twin.

Veno-occlusive disease—Disease caused by blocked veins.

Suggestions for Additional Reading

Except as noted, the following materials are not available from the National Cancer Institute. They can be found in medical libraries, many college and university libraries, and some public libraries. Information about ordering NCI materials is provided at the end of this publication.

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Additional Information

For additional information on this subject, write to the Office of Cancer Communications, National Cancer Institute, Bethesda, MD 20892, or call the toll-free telephone number of the Cancer Information Service at

1-800-4-CANCER*

*In Alaska call 1-800-638-6070; in Hawaii, on Oahu, call 524-1234 (call collect from neighbor islands).

Spanish-speaking staff members are available to callers from the following areas (daytime hours only): California, Florida, Georgia, Illinois, northern New Jersey, New York, and Texas.

The Leukemia Society of America, Inc., is a voluntary health agency that sponsors leukemia research, provides financial aid to patients, and conducts programs in public and professional education about leukemia. For further information, contact your local chapter or the national headquarters, Leukemia Society of America, Inc., 733 Third Avenue, New York, NY 10017.

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